General

Guideline Title

Medications for risk reduction of primary breast cancer in women: U.S. Preventive Services Task Force recommendation statement.

Bibliographic Source(s)

U.S. Preventive Services Task Force (USPSTF). Medications for risk reduction of primary breast cancer in women: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2013 Nov 19;159(10):698-708. [50 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: U.S. Preventive Services Task Force. Chemoprevention of breast cancer: recommendations and rationale. Ann Intern Med. 2002 Jul;137(1):56-8.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

The U.S. Preventive Services Task Force (USPSTF) grades its recommendations (A, B, C, D, or I) and identifies the Levels of Certainty regarding Net Benefit (High, Moderate, and Low). The definitions of these grades can be found at the end of the "Major Recommendations" field.

Summary of Recommendations and Evidence

The USPSTF recommends that clinicians engage in shared, informed decision making with women who are at increased risk for breast cancer about medications to reduce their risk. For women who are at increased risk for breast cancer and at low risk for adverse medication effects, clinicians should offer to prescribe risk-reducing medications, such as tamoxifen or raloxifene. (B recommendation)

See the Clinical Considerations section for additional information about risk factors.

The USPSTF recommends against the routine use of medications, such as tamoxifen or raloxifene, for risk reduction of primary breast cancer in women who are not at increased risk for breast cancer. (D recommendation)

Clinical Considerations

Patient Population Under Consideration

This recommendation applies to asymptomatic women aged 35 years or older without a prior diagnosis of breast cancer, ductal carcinoma in situ

(DCIS), or lobular carcinoma in situ (LCIS). Neither tamoxifen nor raloxifene should be used in women who have a history of thromboembolic events (deep venous thrombosis, pulmonary embolus, stroke, or transient ischemic attack). The USPSTF has issued separate recommendations for women with BRCA gene mutations (available at www.uspreventiveservicestaskforce.org).

Assessment of Breast Cancer Risk

If a family history of breast cancer or a personal history of breast biopsy is found during the usual patient assessment, clinicians may consider further evaluation using a breast cancer risk assessment tool. Risk assessment tools specifically for family history of breast cancer are available elsewhere (www.uspreventiveservicestaskforce.org).

The National Cancer Institute has developed a Breast Cancer Risk Assessment Tool (available at www.cancer.gov/bcrisktool) that is based on the Gail model and estimates the 5-year incidence of invasive breast cancer in women on the basis of characteristics entered into a risk calculator. This tool helps identify women who may be at increased risk for the disease. Other risk assessment models have been developed by the Breast Cancer Surveillance Consortium (BCSC), Rosner and Colditz, Chlebowski, Tyrer and Cuzick, and others.

Examples of risk factors elicited by risk assessment tools include patient age, race or ethnicity, age at menarche, age at first live childbirth, personal history of DCIS or LCIS, number of first-degree relatives with breast cancer, personal history of breast biopsy, body mass index, menopause status or age, breast density, estrogen and progestin use, smoking, alcohol use, physical activity, and diet.

These models are not recommended for use in women with a personal history of breast cancer, a history of radiation treatment to the chest, or a possible family history of mutations in the *BRCA1* or *BRCA2* genes. Only a small fraction of women are at increased risk for breast cancer. Most who are at increased risk will not develop the disease, and most cases will arise in women who are not identified as being at increased risk. Risk assessment should be repeated when there is a significant change in breast cancer risk factors.

There is no single cutoff for defining increased risk. Most clinical trials defined increased risk as a 5-year risk for invasive breast cancer of 1.66% or greater, as determined by the BCPT (Breast Cancer Prevention Trial). At this cutoff, however, many women would not have a net benefit from risk-reducing medications. Freedman and colleagues developed risk tables that incorporate the BCPT estimate of a woman's breast cancer risk as well as her age, race or ethnicity, and presence of uterus.

On the basis of the Freedman risk–benefit tables for women aged 50 years or older (refer to Figures 2 and 3 and Appendix Figures 1 and 2 in the original guideline document), the USPSTF concludes that many women with an estimated 5-year breast cancer risk of 3% or greater are likely to have more benefit than harm from using tamoxifen or raloxifene, although the balance depends on age, race or ethnicity, the medication used, and whether the patient has a uterus.

Assessment of Risk for Adverse Effects

In general, women receiving medications for breast cancer risk reduction are less likely to have venous thromboembolic events (VTEs) if they are younger and have no other predisposition to thromboembolic events. Women with a personal or family history of venous thromboembolism are at higher risk for these adverse effects.

Women without a uterus are not at risk for tamoxifen-related endometrial cancer. Women with a uterus should have a baseline gynecologic examination before treatment with tamoxifen is started, with regular follow-up after the end of treatment.

Medications for Breast Cancer Risk Reduction

Selective estrogen receptor modulators (tamoxifen and raloxifene) have been shown to reduce the incidence of invasive breast cancer in several randomized, controlled trials. Tamoxifen has been approved for this use in women aged 35 years or older, and raloxifene has been approved for this use in postmenopausal women.

The usual daily doses for tamoxifen and raloxifene are 20 mg and 60 mg, respectively, for 5 years. Aromatase inhibitors (exemestane) have not been approved by the U.S. Food and Drug Administration (FDA) for this indication and are therefore beyond the scope of this recommendation.

Tamoxifen is not recommended for use in combination with hormone therapy or hormonal contraception or in women who are pregnant, may become pregnant, or are breastfeeding.

Other Approaches to Prevention

The USPSTF recommendation on risk assessment, genetic counseling, and genetic testing for BRCA-related cancer can be found at www.uspreventiveservicestaskforce.org . Clinical trials of tamoxifen and raloxifene have not been conducted specifically

in women who are BRCA mutation carriers.

Other Resources

The National Cancer Institute provides information about potential ways to prevent cancer, including lifestyle and diet changes (available at www.cancer.gov/cancertopics/pdq/prevention/breast/Patient and www.cdc.gov/cancer/breast/basic_info/prevention.htm).

The USPSTF does not endorse any particular risk prediction model. However, the BCPT model (www.cancer.gov/bcrisktool) and the BCSC model (https://tools.bcsc-scc.org/BC5yearRisk) can be used by clinicians and patients as part of the process of shared, informed decision making. Both models have been calibrated in U.S. populations.

Definitions:

What the U.S. Preventive Services Task Force (USPSTF) Grades Mean and Suggestions for Practice

Grade	Grade Definitions	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer or provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer or provide this service.
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.	Offer or provide this service for selected patients depending on individual circumstances.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I Statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be measured.	Read "Clinical Considerations" section of USPSTF Recommendation Statement (see the "Major Recommendations" field). If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

USPSTF Levels of Certainty Regarding Net Benefit

Definition: The USPSTF defines *certainty* as "likelihood that the USPSTF assessment of the net benefit of a preventive service is correct." The net benefit is defined as benefit minus harm of the preventive service as implemented in a general, primary care population. The USPSTF assigns a certainty level based on the nature of the overall evidence available to assess the net benefit of a preventive service.

Level of Certainty	Description
High	The available evidence usually includes consistent results from well-designed, well-conducted studies in representative primary care populations. These studies assess the effects of the preventive service on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies.
Moderate	The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by factors such as: • The number, size, or quality of individual studies • Inconsistency of findings across individual studies • Limited generalizability of findings to routine primary care practice; and • Lack of coherence in the chain of evidence As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.
Low	The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of:

Level of Certainty	Description
	• The limited number or size of studies • Important flaws in study design or methods • Inconsistency of findings across individual studies • Gaps in the chain of evidence • Findings not generalizable to routine primary care practice; and • A lack of information on important health outcomes More information may allow an estimation of effects on health outcomes.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Breast cancer, ductal carcinoma in situ (DCIS), or lobular carcinoma in situ (LCIS)

Guideline Category

Assessment of Therapeutic Effectiveness

Counseling

Prevention

Risk Assessment

Clinical Specialty

Family Practice

Internal Medicine

Medical Genetics

Oncology

Preventive Medicine

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Public Health Departments

Guideline Objective(s)

- To summarize the current U.S. Preventive Services Task Force (USPSTF) recommendations for the use of medication for risk reduction of primary breast cancer and the supporting scientific evidence
- To update the 2002 USPSTF recommendation on the use of medications for breast cancer risk reduction

Target Population

Asymptomatic women aged 35 years or older without a prior diagnosis of breast cancer, ductal carcinoma in situ (DCIS), or lobular carcinoma in situ (LCIS)

Interventions and Practices Considered

Risk-reducing medications, such as tamoxifen or raloxifene

Major Outcomes Considered

- Key Question 1: In adult women without pre-existing breast cancer, what is the comparative effectiveness of tamoxifen citrate and raloxifene when used to reduce risk for primary breast cancer on improving short-term and long-term outcomes including invasive breast cancer, noninvasive breast cancer, including ductal carcinoma in situ (DCIS), breast cancer mortality, all-cause mortality, and osteoporotic fractures?
- Key Question 2: What are the harms of tamoxifen citrate and raloxifene when used to reduce risk for primary breast cancer?
- Key Question 3: How do outcomes vary by population subgroups?
- Key Question 4: How do benefits and harms affect decisions to use medications to reduce risk for primary breast cancer, concordance, adherence, and persistence?
- Key Question 5: What methods, such as clinical risk-assessment models, have been used to identify women who could benefit from medications to reduce risk for primary breast cancer?

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): A systematic evidence review was prepared by the Oregon Evidence-based Practice Center (EPC), Oregon Health & Science University for the U.S. Preventive Services Task Force (USPSTF) (see the "Availability of Companion Documents" field).

Data Sources

EPC staff searched MEDLINE, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews from inception through 5 December 2012 for relevant English-language studies, systematic reviews, and meta-analyses. EPC staff manually reviewed reference lists of articles, citations in Web of Science and Scopus, and clinical trial registries. EPC staff requested scientific information packets from manufacturers of medications. (The only packet provided was for raloxifene.)

Study Selection

EPC staff developed selection criteria for studies based on the patient populations, interventions, outcome measures, and types of evidence. After an initial review of citations and abstracts, full-text articles of potentially relevant material were retrieved and a second review was conducted to determine inclusion. A second reviewer confirmed results of the initial reviewer, and discrepancies were resolved by team consensus. Results of the search and selection process are provided in the Appendix Figure in the systematic review.

Inclusion criteria for studies of benefits, harms, and subgroup outcomes (key questions 1 through 3) have been fully described in previous publications. For benefits, EPC staff included only double-blind, placebo-controlled or head-to-head, randomized, controlled trials (RCTs) of tamoxifen and raloxifene to reduce risk for breast cancer that enrolled women without preexisting breast cancer. EPC staff included trials that were designed and powered to demonstrate invasive breast cancer incidence as a primary or secondary outcome. For harms, EPC staff included RCTs and observational studies of tamoxifen and raloxifene in women without breast cancer that had a nonuser comparison group or direct comparisons between tamoxifen and raloxifene. All adverse outcomes at all reported follow-up times were considered to capture potential short- and long-term adverse effects.

EPC staff included RCTs, observational studies, and descriptive studies of decisions to use risk-reducing medications, concordance, adherence, and persistence of use (key question 4). Concordance occurs when a health care provider and patient reach a shared agreement about therapeutic goals after the patient is informed of the condition and options for treatment and becomes involved in the treatment decision. Adherence is the extent to which a patient acts in accordance with the prescribed interval and dose of a medication. Persistence is the duration of time from initiation to discontinuation of therapy.

EPC staff included studies of risk-stratification models that could be used in primary care settings to identify women at higher-than-average risk for breast cancer (key question 5). Only studies reporting discriminatory accuracy were included. Discriminatory accuracy is a measure of how well the model can correctly classify persons at higher risk from those at lower risk and is measured by the model's concordance statistic or c-statistic. The c-statistic is determined by the area under the receiver-operating characteristic curve, a plot of sensitivity (true-positive rate) versus 1 – specificity (false-positive rate). Perfect discrimination is a c-statistic of 1.0, whereas a c-statistic of 0.5 would result from chance alone. An acceptable level of discrimination is between 0.70 and 0.79, excellent is between 0.80 and 0.89, and outstanding is 0.90 or greater. EPC staff also abstracted model calibration, a measure of how well predicted probabilities agree with actual observed risk in a population. In a perfect prediction model, the predicted risk in a population would equal the observed number of cases, such that the percentage expected divided by the percentage observed equals 1.0. Studies of individual risk factors or laboratory tests as well as models designed primarily to evaluate risk for deleterious BRCA mutations were excluded.

Search strategies also included systematic reviews that addressed key questions and had similar scope, inclusion criteria, and analytic methods for meta-analysis. Other types of analyses and statistical models were not included.

Number of Source Documents

- Key Questions 1-3: 50 studies
- Key Question 4: 50 studies
- Key Question 5: 21 studies

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Weighting According to a Rating Scheme (Scheme Not Given)

Rating Scheme for the Strength of the Evidence

Not stated

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): A systematic review of the literature was prepared by the Oregon Evidence-based Practice Center (EPC) for use by the U.S. Preventive Services Task Force (USPSTF) (see the "Availability of Companion Documents" field).

Data Abstraction and Quality Assessment

An investigator abstracted details of the patient population, study design, analysis, follow-up, and results. A second investigator confirmed key data elements. Using pre- defined criteria, 2 investigators independently rated the quality of studies (good, fair, or poor) and resolved discrepancies by consensus. Investigators assessed applicability of trials using the population, intervention, comparator, outcomes, timing of outcomes measurement, and setting (PICOTS) format.

Data Synthesis and Analysis

Investigators updated the results of the previous meta-analysis of benefits and harms of tamoxifen and raloxifene for 2 outcomes (mortality and endometrial cancer for raloxifene) with new data using methods described in previous publications. As a group, investigators used methods developed by the USPSTF to assess the overall quality of the body of evidence for each key question (good, fair, or poor) on the basis of the number, quality, and size of studies; consistency of results between studies; and directness of evidence.

Methods Used to Formulate the Recommendations

Balance Sheets

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The U.S. Preventive Services Task Force (USPSTF) systematically reviews the evidence concerning both the benefits and harms of widespread implementation of a preventive service. It then assesses the certainty of the evidence and the magnitude of the benefits and harms. On the basis of this assessment, the USPSTF assigns a letter grade to each preventive service signifying its recommendation about provision of the service (see table below). An important, but often challenging, step is determining the balance between benefits and harms to estimate "net benefit" (that is, benefits minus harms).

Table 1. U.S. Preventive Services Task Force

Certainty of Net Benefit	Magnitude of Net Benefit			
	Substantial	Moderate	Small	Zero/Negative
High	A	B	C	D
Moderate	B	B	C	D
Low	Insufficient			

**A, B, C, D*, and *I (Insufficient)* represent the letter grades of recommendation or statement of insufficient evidence assigned by the U.S. Preventive Services Task Force after assessing certainty and magnitude of net benefit of the service (see the "Rating Scheme for the Strength of the Recommendations" field).

The overarching question that the Task Force seeks to answer for every preventive service is whether evidence suggests that provision of the service would improve health outcomes if implemented in a general primary care population. For screening topics, this standard could be met by a large randomized, controlled trial (RCT) in a representative asymptomatic population with follow-up of all members of both the group "invited for screening" and the group "not invited for screening."

Direct RCT evidence about screening is often unavailable, so the Task Force considers indirect evidence. To guide its selection of indirect evidence, the Task Force constructs a "chain of evidence" within an analytic framework. For each key question, the body of pertinent literature is critically appraised, focusing on the following 6 questions:

1. Do the studies have the appropriate research design to answer the key question(s)?

2. To what extent are the existing studies of high quality? (i.e., what is the internal validity?)
3. To what extent are the results of the studies generalizable to the general U.S. primary care population and situation? (i.e., what is the external validity?)
4. How many studies have been conducted that address the key question(s)? How large are the studies? (i.e., what is the precision of the evidence?)
5. How consistent are the results of the studies?
6. Are there additional factors that assist the USPSTF in drawing conclusions (e.g., presence or absence of dose–response effects, fit within a biologic model)?

The next step in the Task Force process is to use the evidence from the key questions to assess whether there would be net benefit if the service were implemented. In 2001, the USPSTF published an article that documented its systematic processes of evidence evaluation and recommendation development. At that time, the Task Force's overall assessment of evidence was described as good, fair, or poor. The Task Force realized that this rating seemed to apply only to how well studies were conducted and did not fully capture all of the issues that go into an overall assessment of the evidence about net benefit. To avoid confusion, the Task Force has changed its terminology. Whereas individual study quality will continue to be characterized as good, fair, or poor, the term certainty will now be used to describe the Task Force's assessment of the overall body of evidence about net benefit of a preventive service and the likelihood that the assessment is correct. Certainty will be determined by considering all 6 questions listed above; the judgment about certainty will be described as high, moderate, or low.

In making its assessment of certainty about net benefit, the evaluation of the evidence from each key question plays a primary role. It is important to note that the Task Force makes recommendations for real-world medical practice in the United States and must determine to what extent the evidence for each key question—even evidence from screening RCTs or treatment RCTs—can be applied to the general primary care population. Frequently, studies are conducted in highly selected populations under special conditions. The Task Force must consider differences between the general primary care population and the populations studied in RCTs and make judgments about the likelihood of observing the same effect in actual practice.

It is also important to note that one of the key questions in the analytic framework refers to the potential harms of the preventive service. The Task Force considers the evidence about the benefits and harms of preventive services separately and equally. Data about harms are often obtained from observational studies because harms observed in RCTs may not be representative of those found in usual practice and because some harms are not completely measured and reported in RCTs.

Putting the body of evidence for all key questions together as a chain, the Task Force assesses the certainty of net benefit of a preventive service by asking the 6 major questions listed above. The Task Force would rate a body of convincing evidence about the benefits of a service that, for example, derives from several RCTs of screening in which the estimate of benefits can be generalized to the general primary care population as "high" certainty (see the "Rating Scheme for the Strength of Recommendations" field). The Task Force would rate a body of evidence that was not clearly applicable to general practice or has other defects in quality, research design, or consistency of studies as "moderate" certainty. Certainty is "low" when, for example, there are gaps in the evidence linking parts of the analytic framework, when evidence to determine the harms of treatment is unavailable, or when evidence about the benefits of treatment is insufficient. Table 4 in the methodology document listed below (see the "Availability of Companion Documents" field) summarizes the current terminology used by the Task Force to describe the critical assessment of evidence at all 3 levels: individual studies, key questions, and overall certainty of net benefit of the preventive service.

Sawaya GF et al. Update on the methods of the U.S. Preventive Services Task Force: estimating certainty and magnitude of net benefit. Ann Intern Med. 2007;147:871-875. [5 references].

Rating Scheme for the Strength of the Recommendations

What the U.S. Preventive Services Task Force (USPSTF) Grades Mean and Suggestions for Practice

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C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment	Offer or provide this service for selected patients depending on individual circumstances.

Grade	Grade Definitions	Suggestions for Practice
	and patient preferences. There is at least moderate certainty that the net benefit is small.	
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I Statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be measured.	Read "Clinical Considerations" section of USPSTF Recommendation Statement (see the "Major Recommendations" field). If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

USPSTF Levels of Certainty Regarding Net Benefit

Definition: The USPSTF defines *certainty* as "likelihood that the USPSTF assessment of the net benefit of a preventive service is correct." The net benefit is defined as benefit minus harm of the preventive service as implemented in a general, primary care population. The USPSTF assigns a certainty level based on the nature of the overall evidence available to assess the net benefit of a preventive service.

Level of Certainty	Description
High	The available evidence usually includes consistent results from well-designed, well-conducted studies in representative primary care populations. These studies assess the effects of the preventive service on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies.
Moderate	The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by factors such as: • The number, size, or quality of individual studies • Inconsistency of findings across individual studies • Limited generalizability of findings to routine primary care practice; and • Lack of coherence in the chain of evidence As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.
Low	The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of: • The limited number or size of studies • Important flaws in study design or methods • Inconsistency of findings across individual studies • Gaps in the chain of evidence • Findings not generalizable to routine primary care practice; and • A lack of information on important health outcomes More information may allow an estimation of effects on health outcomes.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Comparison with Guidelines from Other Groups

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Peer Review. Before the U.S. Preventive Services Task Force (USPSTF) makes its final determinations about recommendations on a given preventive service, the Evidence-based Practice Center and the Agency for Healthcare Research and Quality send a draft evidence review to 4 to 6 external experts and to Federal agencies and professional and disease-based health organizations with interests in the topic. The experts are asked to examine the review critically for accuracy and completeness and to respond to a series of specific questions about the document. After assembling these external review comments and documenting the proposed response to key comments, the topic team presents this information to the USPSTF in memo form. In this way, the USPSTF can consider these external comments before it votes on its recommendations about the service. Draft recommendation statements are then circulated for comment among reviewers representing professional societies, voluntary organizations, and Federal agencies, as well as posted on the Task Force Web site for public comment. These comments are discussed before the final recommendations are confirmed.

Response to Public Comment. A draft version of this recommendation statement was posted for public comment on the USPSTF Web site from 16 April through 13 May 2013. In response to public comment and in consideration of U.S. Food and Drug Administration (FDA)-approved indications, the USPSTF provided more information about the target patient population for this recommendation. The USPSTF clarified that the recommendation applies to asymptomatic women aged 35 years or older without a prior diagnosis of breast cancer, ductal carcinoma in situ (DCIS), or lobular carcinoma in situ (LCIS). The final recommendation statement further clarifies that raloxifene has been approved for breast cancer risk reduction in postmenopausal women and that other groups of women should not use tamoxifen. The USPSTF reiterated that only a small fraction of women are candidates for and would derive benefit from risk-reducing medications.

The USPSTF also provided a more comprehensive list of breast cancer risk factors and links to additional resources in response to comments, as well as summary tables to help readers understand the risk– benefit balance of these medications, links to online breast cancer risk assessment models, and updated recommendations of other groups.

Comparison with Guidelines from Other Groups. Recommendations for screening from the following groups were discussed: American Society of Clinical Oncology (ASCO), National Institute for Health and Care Excellence, American Cancer Society (ACS), and the Canadian Task Force on Preventive Health Care.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Potential Benefits of Medications for Breast Cancer Risk Reduction

- The U.S. Preventive Services Task Force (USPSTF) found adequate evidence that treatment with tamoxifen or raloxifene can significantly reduce the relative risk (RR) for invasive estrogen receptor (ER)-positive breast cancer in postmenopausal women who are at increased risk for breast cancer.
- A systematic review of clinical trials found that tamoxifen and raloxifene reduced the incidence of invasive breast cancer by 7 to 9 events per 1000 women over 5 years and that tamoxifen reduced breast cancer incidence more than raloxifene (refer to Appendix Table 3 in the original guideline document). Tamoxifen also reduces the incidence of invasive breast cancer in premenopausal women who are at increased risk for the disease.
- Women who are at increased risk for breast cancer are more likely to benefit from risk-reducing medications. In general, women with an estimated 5-year risk of 3% or greater are, on the basis of model estimates (refer to Figures 2 and 3 and Appendix Figures 1 and 2 in the original guideline document), more likely to benefit from tamoxifen or raloxifene. The USPSTF found that the benefits of tamoxifen and raloxifene for breast cancer risk reduction are no greater than small in women who are not at increased risk for the disease.
- In addition to breast cancer risk reduction, the USPSTF found adequate evidence that tamoxifen and raloxifene reduce the risk for nonvertebral and vertebral fractures, respectively, in postmenopausal women.

Potential Harms

Potential Harms of Medications for Breast Cancer Risk Reduction

- The U.S. Preventive Services Task Force (USPSTF) found adequate evidence that tamoxifen and raloxifene increase risk for venous thromboembolic events (VTEs) by 4 to 7 events per 1000 women over 5 years and that tamoxifen increases risk more than raloxifene (refer to Appendix Table 3 in the original guideline document). The USPSTF found that potential harms from thromboembolic events are small to moderate, with increased potential for harms in older women.
- The USPSTF also found adequate evidence that tamoxifen but not raloxifene increases risk for endometrial cancer (4 more cases per 1000 women). Potential harms from tamoxifen-related endometrial cancer are small to moderate and depend on hysterectomy status and age. The potential risks for tamoxifen-related harms are higher in women older than 50 years and in women with a uterus. Tamoxifen may also increase the incidence of cataracts.
- Vasomotor symptoms (hot flashes), a common adverse effect of both medications that is not typically classified as serious, may affect a patient's quality of life and willingness to use or adhere to these medications.

Qualifying Statements

Qualifying Statements

- The U.S. Preventive Services Task Force (USPSTF) makes recommendations about the effectiveness of specific clinical preventive services for patients without related signs or symptoms.
- It bases its recommendations on the evidence of both the benefits and harms of the service and an assessment of the balance. The USPSTF does not consider the costs of providing a service in this assessment.
- The USPSTF recognizes that clinical decisions involve more considerations than evidence alone. Clinicians should understand the evidence but individualize decision making to the specific patient or situation. Similarly, the USPSTF notes that policy and coverage decisions involve considerations in addition to the evidence of clinical benefits and harms.
- Recommendations made by the USPSTF are independent of the U.S. government. They should not be construed as an official position of the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

Implementation of the Guideline

Description of Implementation Strategy

The experiences of the first and second U.S. Preventive Services Task Force (USPSTF), as well as that of other evidence-based guideline efforts, have highlighted the importance of identifying effective ways to implement clinical recommendations. Practice guidelines are relatively weak tools for changing clinical practice when used in isolation. To effect change, guidelines must be coupled with strategies to improve their acceptance and feasibility. Such strategies include enlisting the support of local opinion leaders, using reminder systems for clinicians and patients, adopting standing orders, and audit and feedback of information to clinicians about their compliance with recommended practice.

In the case of preventive services guidelines, implementation needs to go beyond traditional dissemination and promotion efforts to recognize the added patient and clinician barriers that affect preventive care. These include clinicians' ambivalence about whether preventive medicine is part of their job, the psychological and practical challenges that patients face in changing behaviors, lack of access to health care or of insurance coverage for preventive services for some patients, competing pressures within the context of shorter office visits, and the lack of organized systems in most practices to ensure the delivery of recommended preventive care.

Dissemination strategies have changed dramatically in this age of electronic information. While recognizing the continuing value of journals and other print formats for dissemination, the USPSTF Task Force will make all its products available through its Web site . The combination of electronic access and extensive material in the public domain should make it easier for a broad audience of users to access USPSTF materials and adapt them for their local needs. Online access to USPSTF products also opens up new possibilities for the appearance of the annual, pocket-size Guide to Clinical Preventive Services.

To be successful, approaches for implementing prevention have to be tailored to the local level and deal with the specific barriers at a given site,

typically requiring the redesign of systems of care. Such a systems approach to prevention has had notable success in established staff-model health maintenance organizations, by addressing organization of care, emphasizing a philosophy of prevention, and altering the training and incentives for clinicians. Staff-model plans also benefit from integrated information systems that can track the use of needed services and generate automatic reminders aimed at patients and clinicians, some of the most consistently successful interventions. Information systems remain a major challenge for individual clinicians' offices, however, as well as for looser affiliations of practices in network-model managed care and independent practice associations, where data on patient visits, referrals, and test results are not always centralized.

Implementation Tools

Foreign Language Translations

Mobile Device Resources

Patient Resources

Pocket Guide/Reference Cards

Staff Training/Competency Material

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

U.S. Preventive Services Task Force (USPSTF). Medications for risk reduction of primary breast cancer in women: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2013 Nov 19;159(10):698-708. [50 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2002 Jul (revised 2013 Nov 19)

Guideline Developer(s)

U.S. Preventive Services Task Force - Independent Expert Panel

Guideline Developer Comment

The U.S. Preventive Services Task Force (USPSTF) is a federally-appointed panel of independent experts. Conclusions of the USPSTF do not necessarily reflect policy of the U.S. Department of Health and Human Services (DHHS) or its agencies.

Source(s) of Funding

The U.S. Preventive Services Task Force (USPSTF) is an independent, voluntary body. The U.S. Congress mandates that the Agency for Healthcare Research and Quality support the operations of the USPSTF.

Guideline Committee

U.S. Preventive Services Task Force (USPSTF)

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**Members of the U.S. Preventive Services Task Force at the time this recommendation was finalized. For a list of current Task Force members, go to http://www.uspreventiveservicestaskforce.org/Page/Name/our-members*.

Financial Disclosures/Conflicts of Interest

The U.S. Preventive Services Task Force (USPSTF) has an explicit policy concerning conflict of interest. All members disclose at each meeting if they have a significant financial, professional/business, or intellectual conflict for each topic being discussed. USPSTF members with conflicts may be recused from discussing or voting on recommendations about the topic in question.

Disclosure forms from USPSTF members can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M13-1993.

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: U.S. Preventive Services Task Force. Chemoprevention of breast cancer: recommendations and rationale. Ann Intern Med. 2002 Jul;137(1):56-8.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Electronic copies: Available from the Annals of Internal Medicine Web site.

Availability of Companion Documents

The following are available:

Evidence Reviews:

- Nelson HD, Fu R, Humphrey L, Smith MEB, Griffin JC, Nygren P. Comparative effectiveness of medications to reduce risk of primary breast cancer in women. Comparative Effectiveness Review No. 17. AHRQ Publication No. 09-EHC028-EF. Rockville (MD): Agency for Healthcare Research and Quality; 2009 Sep. 144 p.
- Nelson HD, Smith MEB, Griffin JC, Fu R. Use of medications to reduce risk for primary breast cancer: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med. 2013;158(8):604-614.

Electronic copies: Available from the U.S. Preventive Services Task Force (USPSTF) Web site.

Background Articles:

- Barton MB et al. How to read the new recommendation statement: methods update from the U.S. Preventive Services Task Force. Ann Intern Med 2007;147:123-127.
- Guirguis-Blake J et al. Current processes of the U.S. Preventive Services Task Force: refining evidence-based recommendation development. Ann Intern Med 2007;147:117-122.
- Sawaya GF et al. Update on the methods of the U.S. Preventive Services Task Force: estimating certainty and magnitude of net benefit. Ann Intern Med 2007;147:871-875.
- Petitti DB et al. Update on the methods of the U.S. Preventive Services Task Force: insufficient evidence. Ann Intern Med. 2009;150:199-205.

Electronic copies: Available from the USPSTF Web site.

The following are also available:

- Medications for risk reduction of primary breast cancer. Clinical summary of U.S. Preventive Services Task Force recommendation. 2013 Sep. 1 p. Electronic copies: Available from the USPSTF Web site.
- The guide to clinical preventive services, 2012. Recommendations of the U.S. Preventive Services Task Force. Rockville (MD): Agency for Healthcare Research and Quality (AHRQ); 2012. 128 p. Electronic copies: Available from the AHRQ Web site. See the related QualityTool summary on the Health Care Innovations Exchange Web site.
- A continuing medical education (CME) activity is available from the Annals of Internal Medicine Web site.

The Electronic Preventive Services Selector (ePSS) is an application designed to provide primary care clinicians and health care teams timely decision support regarding appropriate screening, counseling, and preventive services for their patients. It is based on the current, evidence-based recommendations of the USPSTF and can be searched by specific patient characteristics, such as age, sex, and selected behavioral risk factors.

Patient Resources

The following are available:

- Understanding Task Force recommendations: medications for the risk reduction of primary breast cancer in women. Consumer fact sheet. 2013 Sep. 4 p. Electronic copies: Available in Portable Document Format (PDF) from the U.S. Preventive Services Task Force (USPSTF) Web site.
- Medications for risk reduction of primary breast cancer: U.S. Preventive Services Task Force recommendation statement. Summary for

patients. Ann Intern Med. 2013 Nov 19;159(10):I-28. Electronic copies: Available from the Annals of Internal Medicine Web site .

- Women: stay healthy at any age. Rockville (MD): Agency for Healthcare Research and Quality. AHRQ Pub. No. 10-IP002-A. 2010 Aug. 2 p. Electronic copies: Available in PDF in English and Spanish from the AHRQ Web site. See the related QualityTool summary on the Health Care Innovations Exchange Web site .

Print copies: Available in English and Spanish from the Agency for Healthcare Research and Quality (AHRQ) Publications Clearinghouse. For more information, go to http://www.ahrq.gov/research/publications/index.html or call 1-800-358-9295 (U.S. only).

Myhealthfinder is a new tool that provides personalized recommendations for clinical preventive services specific to the user's age, gender, and pregnancy status. It features evidence-based recommendations from the USPSTF and is available at www.healthfinder.gov .

NGC Status

This NGC summary was completed by ECRI on June 25, 2002. The information was verified by the guideline developer as June 27, 2002. This NGC summary was updated by ECRI Institute on January 15, 2014. The updated information was verified by the guideline developer on January 22, 2014.

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